specification, for example at page 4 lines 1-5, page 6 at line 12, page 7 at line 5, page 8 lines 5-12, and Examples 1-3. New Claims 21-22 have been added. These Claims include the limitations that intact cells to be counted or detected are isolated and further that the intact cells may be counted and/or detected using flow cytometry or fluorescent microscopy. Support for this amendment is found throughout the specification, for example at page 3 lines 8-10, page 5 line 4, page 10 lines 6-11, page 15 lines 1-5 and Examples 1-3.

PRIORITY/DECLARATION

On page 2 of the Official Action dated October 25, 2002, the Examiner argued that the phrase "This application is related to U.S. Ser. No" is improper. However, a routine search of the U.S. Patent database found that this phrase is commonly used. The phrase "related to U.S. Ser. No" was found in U.S. Patents 4,780,460; 4,992,271; 5,610,289; 5,763,137; 5,827,785; 5,945,659; and 6,210,878. Each of these patents is included in an information disclosure statement attached to this amendment for the Examiner's review.

To be clear, the specification has been amended to clarify that the present application is not a continuation-in-part application.

It is Applicant's position that no new oath is needed as no claim for priority has been made. The Examiner has argued on page 2 of the Official Action dated October 25, 2002 that the oath fails to identify priority documents by application number and filing date. However, no claim to priority documents is made. Therefore, no new oath is needed.

For all of these reasons Applicant's respectively urge the Examiner to remove the objections to the oath and specification set forth in the Official Action dated October 25, 2002.

REJECTION UNDER SECTION 112

Numerous rejections of Claims 18-19 under 35 U.S.C. 112, second paragraph are found in the Official Action dated October 25, 2002. In summary, the Examiner argued:

1) It is unclear how the phrase "whereby said latent viral load is the determined number of cells" correlated with viral load in a host as stated in the preamble.

2) That the phrase "cell population" is unclear as to whether it is uninfected cells.

3) That the preamble recites determining latent viral load in a host but the claim has no language that serves to correlate the result of "determining the number of cells expressing gp120" with "determining viral load".

4) That the phrase "capable of" is unclear.

5) That the cell population is infected cells and cannot be used to determine latent viral load.

6) That the phrase "depleting a cell population comprising" is unclear as to what is being depleted.

With respect to rejection 1, the phrase "in the host" was added to the phrase "whereby said latent viral load in the host is the determined number of cells". The amendment is intended to clarify that the determined number of cells is a measure of latent viral load in the host from which the cells tested were taken.

With respect to the rejections 2, 3, 5 and 6, the phrase "depleting a cell population comprising intact cells susceptible to HIV-infection expressing cell-surface gp120" was amended to "depleting a cell population obtained from the host of cells expressing cell-surface gp120 to obtain a depleted cell population, the original cell population comprising intact cells susceptible to HIV-infection". This amendment is intended to clarify that there are two cell populations. The first is a cell population obtained from the host and a second depleted cell population. The cells of the first cell population should be intact cells and susceptible to HIV-infection. This means that assay cannot be performed on cells that cannot be infected with HIV. The cells that are depleted from the original cell population are those expressing cell-surface gp120, e.g. infected cells. The depletion provides a depleted cell population, which is then used to measure latent viral load.

With respect to the rejection 4, the phrase "capable of activating" was amended to "which activates".

Claims 18 and 19 have been amended as supported by the specification to better clarify the invention. For all of these reasons Applicant's respectively urge the Examiner to remove the rejections to Claims 18-19 set forth in the Official Action dated October 25, 2002.

REJECTION UNDER SECTION 103

The rejection of Claims 1-13, 15-16, and 18-19 under 35 USC 103(a) as being unpatentable over the combination of Chun et al. (Nature 387:183-188 May 1997), hereinafater Chun '97, Chun et al. (Nature Medicine 1(12):1284-1290 Dec 1995), hereinafter Chun '95, and Essex (USPN 4,725,669), hereinafter Essex '669, was maintained for reasons of record. The rejection of Claims 13-19 under 35 USC 103(a) as being unpatentable over the combination Chun "97, Chun '95, Essex '669 and Chun (J. Exp. Med. 188(1):83-91 July 6, 1998), hereinafter Chun '98 was maintained for reasons of record.

The Examiner further argued (Office Action of October 25, 2002) that:

1) The Fields Virology text discloses gp120 is positioned on the external surface of virion membranes as well as plasma membranes of infected cells and therefore the ordinary artisan would have had a high expectation of success in using gp120 as the marker in the differential expression method of Chun et al.

2) The Fessel reference deals with RNA expression and progression of HIV infection and not the expression of viral protein and therefore cannot be applied to the expression of viral proteins.

3) All markers that are unique to the infected state of cell are deemed functional equivalents with regard to determining cell status. Further that one of ordinary skill in

the art would not only be motivated to use a marker that would streamline his methodology, he or she would have a high expectation of success.

4) Both Chun references utilize intact cells.

With respect to 1-3, the Examiner has concluded that any marker for an infected state is interchangeable with each other. Applicants strongly disagree with this statement. Three references are provided in the attached IDS, each with a publication date prior to the filing date of the instant application. Jenny-Avital (AIDS Clin Care. 1999 Mar;11(3):20-1) teaches that viral load testing using the Roche RT-PCR test may not always be accurate measure of progression of disease due to variant subtypes of HIV-1. This reference indicates that variation in the HIV virus may affect the usefulness of some viral makers. Denison R (WORLD. 1999 Apr;(No 96):4-5) teaches that even though women have lower viral loads, women progress to AIDS just as rapidly as men. This indicates that viral load as measured by PCR is a complex indicator of disease progression. Sullivan et al. (AIDS. 1999 Jan 14;13(1):89-96) teaches that in patients with persistently negative antibody tests, HIV infection can be proven by other methods use as nucleic acid amplification, p24 antigen, or viral culture. Based on the literature available described above, the ordinary artisan most certainly does not have a reasonable expectation that all markers of HIV are functional equivalents of each other nor that all markers indicate progression of disease and hence viral load equally well. The art at the time the invention was made teaches that subtype variations may affect test results and variation in viral load between men and women even though men and women have similar disease progressions and that one test may be negative while infection may be proven by different tests. At a minimum the art at the time the invention was made indicates unpredictability in comparing tests using different markers. Further there is no expectation that changing the marker detected in the method of Chun '97 will "streamline" the methodology of Chun as argued by the Examiner. Some tests take significantly longer to perform and would not necessarily "streamline" Chun's method. There is no motivation in any reference cited by the Examiner that would have led the ordinary artisan to have "exchanged" the marker of Chun '97. In fact, the art available to the ordinary artisan at the time the invention was made would have indicated that viral makers cannot be easily "exchanged".

Further, the Fessel reference was provided to demonstrate the unpredictability of a single marker, nucleic acid as a functional marker. In a previous advisory action (April 3, 2001), the Examiner argued that the Fessel reference "was published after the filing date and hence is not indicative of what was known in the art at the time of the invention.". While Applicant's disagree with this conclusion for the reasons of record, the references that are reviewed in the Fessel reference, each of which has an earlier publication date that the filing date of the instant application are provided in the attached IDS for the Examiner's review. These references include Kaufmann et al. (Lancet 1998:351:723-4), Piketty et al (AIDS 1998;12:745-50), Levitz (NEJM 1998, 338:1074-5), and Renaud et al (AIDS 1999, 13:669-76). The Levitz and Piketty references indicate that CD4+ counts can increase despite persistently detectable viral load suggesting that viral load alone may not be a good indicator to change antiretroviral therapy. These results indicate two

markers of disease progression CD4+ counts and viral load are not interchangeable. Together with the other references cited above, the Fessel references contradict the Examiner's assertion that all markers unique for an infected state are interchangeable. Further that what was known in the art at the time the invention was made was that nucleic acid maybe unpredictable indicator of the progression of HIV and hence viral load and further that markers of HIV infection are not functionally equivalent.

With respect to point 4, Applicant disagrees that the methods of Chun '97 and Chun '95 use intact cells in the detection step, as is claimed. The Examiner pointed to Figure 1 and page 1289 of the Chun '95 article. However, what is present in Figure 1 and page 1289 of the reference are methods used by Chun '95 to obtain a purified resting cell population on which to perform activation and analysis. These are not the intact cells of a detection step. Chun '97 and Chun '95 do not use intact cells for a detection step. In fact, as stated on numerous occasions, cells such as those isolated in Figure 1 are activated and then lysed for analysis making it impossible to detect intact cells using the method of Chun '97. In a previous Office Action (July 18, 2000) the Examiner argued "enumeration of cells within culture or used in an assay is a standard laboratory procedure". However, as mentioned above, counting cells in a detection step in the method of Chun '97 and Chun '95 is impossible. No reference has been made of record that discloses counting cells relevant to the method of Chun '97 or Chun '95. Importantly, no teaching that provided any motivation for modifying the method of Chun '97 or Chun '95, even that combined with the teachings of Essex '669 has been made of record. In fact, the method of Chun '97 and Chun '95 cannot be modified to count cells. The method of Chun '97 and Chun '95 is necessarily an indirect measure because the cells used for analysis cannot be counted. The methods of the present invention are a direct cell count of infected cells that remain intact and can be collected for further analysis or use.

Finally, the activators used in the method of Chun '97 are general activators while those of the instant invention are directed to activating HIV integrated into the genome of cells. The Examiner argued in an Office action mailed February 25, 2000 that Chun do not use cytokines to stimulate latent virus production in resting cells but suggested that it would have been obvious to have used the activator of the present invention in the method of Chun but has provided no reference disclosing the activator of the present invention nor provided motivation for changing the activator used by Chun '97.

Claim 1 as amended recites the detection step "counting the cells therein". Neither the methods of Chun '97, Chun '95 nor Essex '669 teach or suggest counting cells in a detection step. Therefore, the combination of references described above cannot render the amended claim obvious.

Claims 18 and 19 have been amended as supported by the specification to recite a detection step including counting a number of intact cells. As mentioned above the methods of Chun '97, Chun '95 or Essex '669 in combination do not teach or suggest counting cells in a detection step.

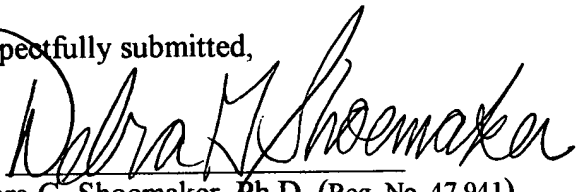
Claims 20-22 are not taught or rendered obvious by any combination of Chun '97, Chun '95 or Essex '669 because neither isolation of cells in a detection step, nor the use of flow cytometry or fluorescent microscopy in a detection step is taught or suggested by these references.

Applicant respectfully requests that the Examiner consider these additional comments. The instant claims as amended are not taught or made obvious by the combination of Chun '97, Chun '95 and Essex '669 nor the combination of Chun '97, Chun '95, Essex '669, and Chun '98 and Applicant respectfully respects the withdrawal of the rejections.

Consideration and allowance of Claims 1-13, 15-16, 18-21 are respectfully requested. The Examiner is urged to contact Applicant to advance the prosecution of this application.

Attached hereto is a marked-up version of the changes made to the specification by the current amendment. The attached paged are captioned "**Version with markings to show changes made**."

Respectfully submitted,

By: 

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

IN THE CLAIMS:

Please amend the claims as follow:

1. (Twice Amended) A method of determining the latent viral load in a host infected with HIV comprising,

contacting resting lymphoid mononuclear cells obtained from the host with an effective amount of an agent which activates an HIV virus integrated into the genome of the cells; and

detecting the expression of cell-surface gp120 on intact cells after the cells have been contacted with the agent and [determining the number of] counting the intact cells therein, wherein the number of intact cells expressing cell-surface gp120 is a measure of latent viral load.

18. (Twice Amended) A method of determining latent viral load in a host infected with HIV comprising,

depleting a cell population obtained from the host of cells expressing cell-surface gp120 to obtain a depleted cell population, the original cell population comprising intact cells susceptible to HIV-infection [expressing cell-surface gp120], and

counting [determining], in said depleted cell population, the number of intact cells expressing cell-surface gp120, wherein said depleted cell population has been contacted with an agent which activates [capable of activating] HIV integrated into the genome of said cells under conditions effective for said agent to activate integrated HIV to obtain a determined a number of cells,

whereby said latent viral load in the host is the determined number of cells.

19. (Twice Amended) A method of determining latent viral load in a host infected with HIV comprising,

depleting a cell population obtained from the host of cells expressing cell-surface gp120 to obtain a depleted cell population, the original cell population comprising intact cells susceptible to HIV-infection [expressing cell-surface gp120],

contacting said depleted cell population with an agent which activates [capable of activating] HIV integrated into the genome of said cells under conditions effective for said agent to activate integrated HIV, and

counting [determining], in said depleted cell population, the number of intact cells expressing cell-surface gp120 to obtain a determined a number of cells,

whereby said latent viral load in the host is the determined number of cells.